NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC SWITCH

EXECUTIVE SUMMARY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 21, 1999

FROM: OTC Flexeril Review Team

TO: Advisory Committee Members

SUBJECT: July 20, 1999 Advisory Committee Meeting to discuss proposed Rx to OTC switch for Flexeril (cyclobenzaprine hydrochloride)

Summary of Issues from FDA Reviews

The purpose of this memorandum is to provide pertinent background summary information and to raise points to consider as you prepare for the upcoming meeting on July 20, 1999. The package that you have been provided contains the draft agenda, reviews and draft questions that will be addressed. Some reviews that will not be presented have been provided for additional information and will be identified as such.

Background

Flexeril (cyclobenzaprine hydrochloride) has been marketed in the United States since 1977 as a prescription drug for the relief of acute temporary muscle spasm caused by local trauma or strain. It was approved as 5 mg and 10 mg tablets, to be taken in divided doses for a total dose of 20-40 mg a day. Cyclobenzaprine is structurally related to the tricyclic antidepressants and has some properties in common with this class such as antimuscarinic effects, associated with significant sedation, confusion, and transient visual hallucinations in some individuals.

Merck & Co., Inc.'s application for an over-the-counter switch of Flexeril was submitted on December 19, 1998. The proposed indication for the switch is for the relief of painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury. A dosage of 5 mg every 6 to 8 hours (not to exceed 3 tablets every 24 hours) for as long as symptoms remain, but not to exceed 10 consecutive days of use, has been proposed. If approved, Flexeril

would be the first muscle relaxant available without a prescription in the United States.

The Agency has previously sought advice from scientists and consumer representatives on issues regarding OTC availability of muscle relaxants. On December 7, 1990, the Arthritis Advisory Committee discussed issues pertaining to OTC marketing of an OTC muscle relaxant. On March 28, 1995, a combined meeting of the Arthritis Advisory Committee and the Non-Prescription Drug Advisory Committee discussed the entire spectrum of muscle relaxants. The March 28, 1995 meeting included presentation of summary background information from the Clinical Practice Guideline – Acute Low Back Problems in Adults (published by the U.S. Department of Health and Human Service, Agency for Health Care Policy and Research, December 1994, in Attachment 1), as well as a general discussion of muscle relaxant drugs and their properties. The committee at that time felt that these products were potentially useful in the armamentarium of therapy for acute low back pain with spasm; however, concern was raised as to the appropriateness of OTC availability of these products. The Agency has recently been engaged in discussions with Merck, regarding Merck's interest in developing a Flexeril product for the OTC marketplace.

As noted in the sponsor's package and in the FDA reviews contained within this package, there are several issues that have been targeted for discussion.

Specific Issues

1. Efficacy

There were 13 trials submitted in NDA 21-070 to support the OTC switch of Flexeril: 4 studies addressed clinical pharmacology/pharmacokinetic issues, 6 studies addressed psychomotor aspects; and 3 studies addressed clinical efficacy (with evaluation of short-term safety in 2 of these studies, studies P-006 and P-008, and evaluation of OTC actual use in 1 study, study P-009).

Protocols (P) 006 and 008 were similar in design, each having three treatment arms (P-006 with Flexeril 10, Flexeril 5 and placebo; P-008 with Flexeril 5, Flexeril 2.5 and placebo), employing a 7-day dosing regimen, and utilizing the same three primary efficacy endpoints (patient-rate global impression of change, patient rating of medication helpfulness, and a diary card questioning relief from starting backache; all patient-derived measures, using five-point scales). One of the secondary variables was a physician rating of muscle spasm throughout the study, also on a five-point scale. Concomitant analgesic usage was not allowed. The sponsor-generated, pre-specified analysis, revealed that Flexeril 5 mg was statistically significantly better than placebo for three primary and all secondary endpoints for P-006 and P-008 at visit 3, but only for P-006 at visit 2.

2. Actual Use

Protocol P-009 was designed as the actual use study. This open-label, multi-dose trial was an attempt to mimic patterns of use in subjects with self-diagnosed muscle spasm, taking Flexeril 5 mg T.I.D. for a period of 7 days. There was no physician verification of the patient's self-diagnosis of spasm. Efficacy was not specifically obtained, but participants were asked to give a global assessment of relief at the end of the trial. The compliance rate with dosing instructions was 73%. Reasons for non-compliance included: use of other medications that were not permitted in the study protocol, use of higher doses of medication, and dosing for a longer time frame than specified in the study protocol.

3. Label Comprehension

The objectives of the Flexeril label comprehension study were to assess: 1) consumer comprehension of label directions, warnings, and uses, 2) accuracy of consumer self-selection for use, and 3) consumer ratings of appropriateness of use for various conditions. The package insert was also evaluated to investigate whether or not it affected comprehension of use and warning information.

Four hundred (400) participants, including 102 participants 65 years or older and 48 participants with less than a high school education, were recruited in 14 geographically distributed shopping malls across the U.S. Participants who had suffered back or neck pain in the last 12 months, and who had used prescription medication for back or neck pain at some time (past or present) were recruited.

The primary questionnaire included multiple choice, yes/no, and open-ended questions. After being screened for eligibility, participants were provided with a picture of the product's front label and instructed to carefully look it over. After participants had read the front label, the back product label was provided, with instructions to carefully look it over as if they were considering buying the product for their own use. The package insert was provided after participants had answered the first 18 questions, pertaining to their perceptions after examining the package labeling.

The results were analyzed by age (18 to 64 vs. 65 and over) and education level (less than high school graduate vs. high school graduate or more). Based on the pattern of results, there are concerns that respondents do not understand that Flexeril: (1) works differently than pain relievers (30% incorrect), (2) can be taken concomitantly with pain relievers (68% incorrect), (3) does not provide relief on the first day of use (52% incorrect), and (4) should only be used for back or neck pain due to recent strain, overuse or injury (49% to 79% incorrect). Forty-two percent

(42%) of respondents aged 65 and over incorrectly indicated they could use Flexeril without first speaking to a doctor (as stated on package labeling and in the package insert). Between 28% and 49% of respondents aged 65 and over indicated they would use Flexeril for inappropriate conditions (e.g., back or neck pain caused by arthritis, leg cramps, arthritis in the knees).

In general, respondents understood that Flexeril should be used for back or neck pain due to recent muscle strain (96% correct), overuse (94% correct), or spasm of back or neck due to strain, overuse or injury (94% correct), understood that for certain conditions, a doctor should be consulted before use (80% to 95% correct), and understood the potential for side effects related to drowsiness (96% to 98% correct). Respondents also demonstrated good comprehension of the maximum daily dose and maximum consecutive dosing (88% to 91% correct). In some cases the package insert increased comprehension above that shown with the label alone (e.g., consumers aged 65 and over should consult a doctor before use).

The combination of these results may indicate that individuals expect Flexeril to act like an analgesic and use it in accordance with their expectations for that type of product. There is concern that this expectation may lead to situations in which consumers who do not received immediate relief either overdose or stop using the product because they believe it does not work. There is also concern that elderly consumers may misuse the product for inappropriate indications such as arthritis in the knees and leg cramps. These issues are of concern in determining whether consumers will be able to use this product effectively and with adequate safety.

4. Pharmacokinetics

Cyclobenzaprine reaches peak concentration in 4 to 5 hours, and it is mostly metabolized with an effective half-life of about 18 hours. The potential for effects of food on absorption has not been investigated. Based on *in vitro* studies, *N*-demethylation appears to be primarily mediated by cytochrome P450 3A4 and 1A2, with a minor role for 2D6. However, these studies were done using *in vitro* concentrations of cyclobenzaprine that were about 2000-fold higher than peak *in vivo* plasma concentrations, so they are not definitive. Also, it appears that there may be significant metabolic pathways other than *N*-demethylation.

Studies in the elderly found 70 to 80% higher plasma concentrations as a reflection of the longer effective half-life (33 hours vs. 18 hours in young subjects). Studies in mild hepatic impairment showed about a doubling of AUC and Cmax in males, but essentially no effect in females (however interpretation is complicated by atypically high concentrations in the healthy female group in the study). There is little information on the pharmacokinetics in moderate or severe hepatic impairment. An effect of gender on cyclobenzaprine pharmacokinetics is not evident, although the sensitivity of this analysis was reduced by intersubject variability.

Drug interaction data are limited. *In vitro* studies suggest little potential for cytochrome P-450 inhibition, but the reporting of these results is as yet incomplete. *In vivo* studies found no significant interaction with aspirin and found conflicting results with diflunisal. No other *in vivo* investigations to evaluate for possible drug interactions have been provided. Protein binding is high (~93%) indicating a possibility of drug interactions through drug displacement. There has been a published case report suggesting that co-administration of cyclobenzaprine and fluoxetine resulted in QT prolongation.

5. Safety

The safety data base included all adverse events which were reported to have occurred in 2,101 participants from the 13 clinical trials contained within this application. The information generated from these studies is consistent with the known adverse event profile for Flexeril as a prescription product. The most frequently reported adverse events in the clinical trials were somnolence, dry mouth, headache, asthenia/fatigue, nausea, and dizziness, the majority of which appear to be dose-dependent. Although post-hoc analysis of gender-related adverse events failed to reveal any differences, there were insufficient numbers of elderly and insufficient ethnic populations to draw meaningful conclusions.

Also submitted were an analysis of 968 postmarketing adverse event reports collected from worldwide safety monitoring, and a review of the literature pertaining to cyclobenzaprine safety. Sixty-six out of the 968 adverse event reports were attributed to drug overdoses with cyclobenzaprine (see Abuse/Misuse below). Of the remaining 902 adverse event reports, 186 were coded as serious adverse events associated with the use of cyclobenzaprine such as seizures, tachycardias and arrhythmias, hallucinations, and pyschosis. There were also 51 case reports of deaths associated with the use of cyclobenzaprine: 12 were due to accidental or intentional overdoses with the drug; 8 occurred in patients $\geq$ 65 years of age; and 5 were reports of fetal deaths following in utero exposure. The remainder of the deaths were attributed to underlying medical conditions, such as heart disease, or to concomitant use of other drugs: central nervous system depressants, mono-amine oxidase inhibitors (MAOIs), and other tricyclic antidepressants, and alcohol. Addditionally, 36 deaths were reported directly to the agency's Spontaneous Reporting System from cylcobenzaprine products, not accounted for in the totals above.

Review of the literature reveals reports of hyperpyretic crisis and deaths associated with the use of cyclobenzaprine and MAOIs; 4 cases of seizures with the cocncomitant use of tramadol hydrochloride; and reports in the elderly of increased risk for developing adverse events related to the drug's anticholinergic effect.

a. Potential for Psychomotor Adverse Effects

The sponsor submitted six studies to assess the psychomotor potential of Flexeril (protocols 001, 002, 003, 012, 014, and 105). Studies 001, 002, and 003 were double-blind trials comparing the sedative and cognitive effects of cyclobenzaprine with diphenhydramine (001 and 003) and placebo, using varying doses of Flexeril (2.5 mg to 5 mg T.I.D. for 10 doses). All three studies demonstrated both significant drowsiness and cognitive/impairment beginning at doses of 2.5 mg, which is also seen persisting through day 4 (with 10 doses of 5 mg T.I.D.). Study 012, a double blind, multi-dose crossover, placebo controlled trial investigating the sedative effects of cyclobenzaprine, clemastine and diphenhydramine in 28 healthy volunteers, demonstrated that cyclobenzaprine was more sedating than both diphenhydramine and placebo with repeated dosing. Study 014, a double blind, multiple-dose, crossover, placebo-controlled study investigating the effects of cyclobenzaprine, diphenhydramine and amitriptyline on driving-related psychomotor skills in elderly volunteers, provided further evidence that cyclobenzaprine is sedating and negatively effects psychomotor function. Study 015 is similarly designed to 014 with the exception of being done in young volunteers. Sedation was most noticeable in the first few doses, with individuals becoming habituated to the sedating properties over time.

All six studies showed significant sedation and psychomotor impairment, at a statistically significant level (p of <0.10). These studies demonstrate the peak sedative effect and (thus psychomotor impairment) for Flexeril occurs 4-6 hours after dosing.

b. Abuse/Misuse

The abuse potential of cyclobenzaprine has not been studied by the standard preclinical assessment studies (drug discrimination, self-administration and dependence studies) that are usually recommended and used in the evaluation of new drugs. Available information on abuse and misuse was obtained from The Drug Abuse Warning Network (DAWN), FDA Adverse Events Reporting System (AERS), Toxic Exposure Surveillance System (TESS), and American Association of Poison Control Centers (AAPCC) data. The frequency of emergency department (ED) mentions relative to the total number of prescriptions for 1992-1997 for cyclobenzaprine is approximately 4 mentions per ten thousand prescriptions, which is less than for carisoprodol or diazepam. The primary reason for the ED visit was for overdose (88.2%) with the motive of committing suicide (74%); other reasons included: dependence (3.5%), recreational use (1.4%) and for other psychic effects (10.8%). In addition, concomitant substance use included alcohol (36.1%) and occasionally other drugs of abuse (e.g., amphetamine, heroin, oxycodone, hydrocodone, hydromorphone, methamphetamine, and marijuana) all <0.1%. Other drugs associated with deaths for cyclobenzaprine were alcohol (33), heroin/morphine (31), cocaine (25), and other opiates.

In the AAPCC database, suicide attempt was by far the largest reason that resulted in a toxic exposure to cyclobenzaprine. Approximately 6 to 8 % of suicide attempt reports involved teenagers.

By far the major concerns with Flexeril center around the misuse and concomitant use with alcohol and other recreational drugs. This was identified in all of the databases reviewed.

Points to Consider

The available data pertinent to the proposed OTC availability of Flexeril will be the discussed at this advisory committee meeting. While Flexeril has been marketed as a prescription product since 1977, for use as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions, there are a number of concerns regarding OTC availability that will be discussed today.

1. The data in the original NDA support the use of a Flexeril dose of 10 mg T.I.D. (in the range of 20-40 mg total daily dose) as a prescription product. In the current submission for OTC use, do both Study 006 and Study 008 demonstrate a clinically significant effect of Flexeril 5 mg T.I.D. for relief of painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury? In answering this question please describe the end-points and analyses that caused you come to your conclusion.

2. Is muscle spasm of the back or neck a consumer self-diagnosable condition? In answering this question please describe the data relied upon from the application.

3. Can consumers identify when Flexeril should be used, as opposed to other products such as an OTC analgesics?
   a) Can they adequately assess whether their condition is responding to treatment?
   b) Were there conditions identified by a significant number of subjects where Flexeril use was considered when it should not have been?

4. Has the metabolism and excretion of Flexeril been adequately characterized?
   (a) If no, what additional information should be obtained (e.g. better characterization of the metabolic pathway, drug-drug interactions)?
   (b) Are there any potential or known drug-drug or drug-food interactions that may impact on the safe use of this drug in the OTC setting?

5. Safety concerns include the adverse reactions associated with Flexeril use (especially adverse reactions similar to those seen with closely-related tricyclic

antidepressants); the possibility of misuse or overdose; and any possible drug interactions.

(a) Can consumers, including elderly individuals, safely use Flexeril in an OTC setting, taking into account the available data on adverse effects, sedation, overdose and misuse, and concomitant medications?
(b) If not, why not? If yes, is any additional information needed on the labeling?

6. Does the Committee have any additional concerns/issues?